REMARKS

Claims 1-20 were previously cancelled. Claims 21-29 are newly cancelled in favor of newly introduced claims 30-35. No new matter is presented by virtue of the within amendments; support therefor can be found throughout the specification and original claims of the application. For instance, new claims 30 and 31 correspond substantially to former claim 25. In particular, claim 30 recites the subject matter of former claim 25 with an added feature described on page 15, lines 5-13 of the present specification. Claim 30 also finds support in former claim 28. Likewise, claim 31 recites the subject matter of former claim 25 with an added feature described on page 15, lines 14-17.

A Request for Continued Examination is being filed concurrently herewith. Accordingly, further examination of the application, as amended, is requested in view of the remarks which follow.

Turning to the Final Office Action, claims 21-29 stand rejected under 35 USC §103(a) over Kawada (1998) and Aoki et al. (1998).

The Examiner asserts at page 3 of the Office Action: "the ordinary artisan would have combined a successful cell culture system to achieve optimal condition for the cells (Kawada et al.) and would have particularly used a cell line known to successfully express HCV (Aoki et al.)."

The rejection is traversed. The cited documents, even in combination, fail to teach or suggest the features of the present invention and cannot therefore sustain the rejection.

Additionally, without acquiescing to the grounds asserted for the rejection, the claims of the application have now been amended to further define and clarify the features of the invention. New claims 30 and 31 recite additional method steps whereby the human hepatocyte can be infected with hepatitis C virus more efficiently. Kawada et al. and Aoki et al. do not teach or suggest such steps.

New independent claim 30 recites:

A method for proliferating a hepatitis C virus comprising the steps of:

providing a radial flow bioreactor which contains in a culture vessel as a main body thereof a porous carrier carrying an immobilized human hepatocyte thereon, which bioreactor can generate a continuous stream of a culture medium in radial direction in said vessel;

infecting said human hepatocyte with a hepatitis C virus, an infectious clone RNA thereof, or a combination thereof;

culturing said human hepatocyte by maintaining a stream of the culture medium in radial direction in said vessel, thereby proliferating the hepatitis C virus in said human hepatocyte,

wherein said infection of hepatitis C virus is carried out by adding hepatitis C virus to said culture medium, and said method further comprises the following steps: circulating the culture medium without supplying fresh medium after adding hepatitis C virus into said culture medium; stopping circulation of the culture medium; and circulating the culture medium without supplying fresh medium.

New independent claim 31 recites:

A method for proliferating a hepatitis C virus comprising the steps of:

providing a radial flow bioreactor which contains in a culture vessel as a main body thereof a porous carrier carrying an immobilized human hepatocyte thereon, which bioreactor can generate a continuous stream of a culture medium in radial direction in said vessel;

infecting said human hepatocyte with a hepatitis C virus, an infectious clone RNA thereof, or a combination thereof;

culturing said human hepatocyte by maintaining a stream of the culture medium in radial direction in said vessel, thereby proliferating the hepatitis C virus in said human hepatocyte,

wherein said infection of hepatitis C virus is carried out by adding hepatitis C virus to said culture medium, and said method further comprises the step of increasing a supply rate of fresh medium and a supply rate of oxygen before adding hepatitis C virus to said culture medium.

As stated above, the instant invention teaches a method whereby the human hepatocyte can be infected with hepatitis C virus more efficiently. Applicants direct the Examiner to the specification, at page 15, lines 5 – 18, which teaches the novel method

steps as recited in claims 30 and 31 (e.g. the steps of circulating the culture medium without supplying fresh medium after adding hepatitis C virus into said culture medium; stopping circulation of the culture medium; and circulating the culture medium without supplying fresh medium (claim 30), and the step of increasing a supply rate of fresh medium and a supply rate of oxygen before adding hepatitis C virus to said culture medium (claim 31)), and not taught by the Kawada or Aoki references:

> After the hepatitis virus-containing liquid culture medium is supplied, further, the supply of fresh one of the liquid culture medium or the circulation of the liquid culture medium is stopped, preferably for about 2 to 24 hours, more preferably for about 2 to 10 hours after the supply of the hepatitis virus-containing liquid culture medium; and while fresh one of the liquid culture medium is not supplied preferably for about 2 to 48 hours, more preferably for about 6 to 48 hours thereafter, the liquid culture medium discharged from the top of the main bioreactor unit 12 is preferably supplied again as a liquid culture medium into the main bioreactor unit 12. In such manner, the infection possibility of hepatitis virus can be increased. For about 15 minutes to 4 hours, preferably about 30 minutes to 2 hours immediately prior to the infection with hepatitis virus, additionally, the velocity of fresh liquid culture medium supply and the velocity of oxygen supply till then are preferably increased to about 1.5-fold to 4-fold, preferably about 1.5-fold to 2.5-fold for culture. In such manner, the possibility of infection with hepatitis virus can be increased, while the cell state can be retained well.

The Examiner argues that "Kawada et al. teach a radial flow bioreactor coupled with a highly functional liver cell line (and) the continuous flow of media generates a beneficial concentration of oxygen and nutrients while preventing excessive shear stresses or build up of waste products." (Office Action, p.2).

The radial flow bioreactor taught by the Kawada reference was made "to overcome many of the ALSS (artificial liver assist systems) problems through the use of a vertically extended cylindrical bed matrix…through which liquid medium flows continuously…this continuous flow through the matrix generates a beneficial concentration gradient of oxygen and nutrients while preventing excessive shear stresses or buildup of waste products." (p.110). The Kawada reference, thus, teaches

a system specifically designed for "high density, large scale cell cultures with long-term viability" (p.110) and nowhere teaches or suggests a system designed for proliferating HCV or any virus. Nowhere in the Kawada reference is there teaching of circulating the culture medium without supplying fresh medium, stopping circulation of the culture medium, and then circulating the culture medium without supplying fresh medium for any reason. Nowhere in the Kawada reference is there teaching of increasing a supply rate of fresh medium.

The addition of the Aoki reference does not cure the defects of the Kawada reference. The Kawada and Aoki references, even in combination, fail to teach or suggest the features of the present invention.

For at least the reasons set forth herein, Applicants respectfully submit that a *prima facie* case of obviousness has not been established under the requirements of 35 U.S.C. § 103(a). To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings (*In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)). Second, there must be a reasonable expectation of success. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicants' disclosure. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 180 U.S.P.Q. 580 (C.C.P.A. 1974).

Accordingly, Applicants respectfully request that the rejection be reconsidered and withdrawn.

CONCLUSION

In view of the above amendments and remarks, Applicant believes the pending application is in condition for allowance.

FEE AUTHORIZATION

A request for continued examination is being filed concurrently herewith. The Commissioner is authorized to charge the fees associated with this submission (including the fees for the request for continued examination) to our Deposit Account, No. 04-1105, Reference 56972(303842). Any overpayment should be credited to said Deposit Account.

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Respectfully submitted,

By /Christine C. O'Day/
Christine C. O'Day
Registration No.: 38,256
EDWARDS ANGELL PALMER & DODGE LLP
P.O. Box 55874
Boston, Massachusetts 02205
(617) 517-5558
Attorneys/Agents For Applicant